## DETAILED ACTION

The amendment filed 1/31/2008 has been received, entered and carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 7, 9-10, 22-25 and 27 have been canceled.

2. Claims 1-2, 8, 12 and 14-18 have been amended.

3. Remarks drawn to objections and rejections under 35 USC 112, first and second paragraphs, 102 and 103.

Claims 1-6, 8, 11-21 and 26 are pending in the case.

### *Specification*

The objection to the abstract has been overcome by amendment.

### *Drawings*

The objection to the drawings has been overcome by amendment.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claims 20-21 under 35 U.S.C. 112, first paragraph, because the specification while being enabling for the treatment and diagnosis of cancer does not

reasonably provide enablement for the diagnosis and treatment of infection by microorganisms, is being maintained for reasons of record.

Applicants have traversed the rejection by arguing that:

1. A reference to a poster presented at a Symposium which shows that the cobalamin complexed to $^{99m}$Tc accumulates in microorganisms causing infections and hence the compounds of this invention can be used in a method of diagnosis and treatment of infections by microorganisms.

2. With respect to the state of the art the Morgan reference is directed to derivatives binding to TCII. The derivatives of the instant invention do not bind to TCII.

3. Since the instant compounds accumulate in the microorganisms their usefulness for treating infections is neither dependent on the particular type of infection nor the particular organism.

4. No further experimentation is needed to make or use the instant invention.

Applicants' arguments are not found to be persuasive.

The reference to the poster session shows that the instant compound accumulates in Staphylococcus aureus. This is just one type of microorganism for which accumulation is shown. One of skill in the art will not extrapolate this to all other microorganisms. Accumulation need not necessarily be to the same extent in all microorganisms. There are no representative examples of a cobalamin conjugated to an antibiotic showing that it accumulates in the microorganism(s) and kills it. Moreover, the Symposium reference states that further studies are needed to evaluate the value radiolabelled cobalamin derivatives for imaging purposes. This means that the inventors are admitting that more experimentation is needed even for imaging purposes, let alone treating infections. The

instant claims are drawn to cobalamin derivatives that have some binding to TCII (less than 20%). Hence, the Morgan reference directed to derivatives binding to TCII is relevant. Applicants' arguments and the supporting reference provided are not seen to overcome the enablement rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of Claims 1-21 and 26-27 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been overcome by amendment of instant claim 1 and cancellation claim 27.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of Claims 1-5, 7-9, 12-13, 19, 21 and 27 under 35 U.S.C. 102(b) as being anticipated by Morgan et al (WO 95/27723; document AJ in IDS of 06/21/2006) has been overcome in view of amendments to the claims, which now recite specific structures for the spacer- chelator groups and applicants' arguments. Morgan does not specifically teach or suggest such groups.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8, 11-21 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morgan et al (WO 95/27723; document AJ in IDS of 06/21/2006) in view of Grissom et al (US 6,797,521) and Collins (US 5,739,313), all of record, necessitated by amendment.

Applicants have traversed the rejection by arguing that:

1. Morgan fails to teach cobalamin derivatives comprising the spacer chelator groups as recited in claim 1. Morgan teaches cobalamin derivatives that bind to TCII. It is not obvious that cobalamin derivatives that do not bind to TCII will have improved selectivity for accumulation in tumor cells and microorganisms.

2. Grissom discloses fluorescent cobalamins for diagnosis of cancer cells. Collins teaches chelating vitamin B12 with detectable radionuclides but both references are silent whether there are particular aspects important for cancer treatment and treatment of infections by microorganisms such as binding to TCII.

Applicants' arguments have been considered but are not found to be persuasive.

Morgan teaches cobalamin derivatives, pharmaceutical compositions and their use in a method of treating neoplastic diseases. However, Morgan et al do not teach or exemplify a cobalamin derivative carrying a radioactive metal, but does suggest the use of radioisotopes conjugated the cobalamin (page 36, lines 20-24). In addition to the teaching above, Morgan also teaches different types of linkers (or spacers) that can be homobifunctional, heterobifunctional, trifunctional that can be used to couple other molecules. The linkers have typically 6 to 30 atoms in the chain and the atoms can be C, N, O or S. Diaminoalkyl, aminoalkyl carboxylic acids, diaminoheteroalkyl and diaminoheteroalkylaryl including pyridyl groups can also be used (page 14 through page 18). One of skill in the art will recognize from this teaching that such bifunctional groups in addition to acting as linkers/spacers can also chelate metal ions and hence act as spacer-chelators. One of skill in the art also knows that if more of such heteroalkyl and heteroaryl chelators are present higher concentrations of metals can be chelated. Morgan

suggests the attachment of chloroquine (a therapeutic agent) to the cobalamin (figure 6; page 54, example 11). Chloroquine has the structural feature that closely resembles the chelators as instantly claimed. Even though chloroquine is used by Morgan as a dye, one of skill in the art will recognize that it can also function as a chelator based on the other chelators suggested.

Grissom, drawn to cobalamin, discloses that radioactively labeled cobalamins are used diagnostic assays (col. 9, lines 10-16).

Collins, drawn to cobalamin, teaches the use of radionuclide labeled cobalamins that also have chelators/linkers attached to them (col. 3, line 5 through col. 6, line 51). Several radioisotopes are suggested for use including some of those recited in instant claims 11 and 14. A variety of homobifunctional and heterobifunctional linking reagents known in the art can be used as linkers (col. 4, lines 20-34). The cobalamins can have cyano, methyl adenosyl groups attached to the central cobalt atom (col. 3, line 65 through col. 4, line 1). The cobalamins are useful for imaging and targeting tumors (col. 3, lines 47-52).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make cobalamin derivatives as instantly claimed and use them in a method of treating and diagnosing neoplastic diseases since the use of such analogous derivatives for the same purpose is seen to be taught in the prior art.

One of skill in the art would be motivated to make the derivatives and use them in a method as instantly claimed inorder to look for potentially better derivatives that diagnose cancer cells and treat them without affecting healthy cells.

***Conclusion***

Claims 1-6, 8, 11-21 and 26 are rejected

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang, Ph.D./
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